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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,896	RABINOVSKY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-16,25,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-24, 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of Record is now **Thaian N. Ton of Art Unit 1632.**

Applicants' Amendment, filed 12/4/06 is compliant and has been entered. Claims 1-40 are pending; claims 17-24 are amended; claims 1-16, 25, 39 and 40 are withdrawn; claims 17-24 and 26-38 are under current examination.

Applicants did not submit any substantive remarks with the Amendment, filed 12/4/06, therefore, the Examiner addresses Applicants' arguments filed 9/5/06, with regard to the rejections of record.

Election/Restrictions

Applicant's election of claims 17-38 (group II), SEQ ID NO:1 and stimulating angiogenesis as the goal of the claimed treatment method in the response on 2/2/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16, 25, 39 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Objections

The prior objection of claims 17-24 and 26-38 as being drawn to a non-elected invention is withdrawn in view of Applicants' amendment to the claims.

Claims 34-36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is a new objection, which is necessitated by Applicants' amendment to the claims. In particular, claim 34 recites delivery of the nucleic acid expression construct

initiates expression of the encoded IGF-I or functional biological equivalent thereof; claim 35 recites that the IGF-I is expressed in tissue specific cells of the subject; claim 36 recites that the tissue specific cells comprise muscle cells. However, Applicants have amended claim 17 to recite that delivery of the nucleic acid expression construct to muscle tissue enables *in vivo* expression activity for the encoded IGF-I or functional biological equivalent thereof. Therefore, claims 34-36 fail to further limit the now-amended claim 17.

Specification

The objection to the specification is maintained. In particular, Applicants have now amended the lines 9-12 of p. 48, ¶162 to recite that the secretion of the transgene produced into the general circulation does not affect myogenin expression in the treated muscle. Applicants state the title of Figure 6, recites "Induction of myogenin" shows that the this is a typographical error, and that amending paragraph 162 to recite "myogenin" is now consistent Figure 6's legend.

This is not fully persuasive. In particular, ¶ 162, lines 1-3 recites that, "Additional experiments were done to determine the effects of IGF-I plasmid mediated supplementation using a construct that stimulates the secretion of the transgene product into the general circulation on *MyoD* expression after a nerve injury." Thus, it appears that either lines 9-12 of this paragraph do not relate back to the experiments with regard to MyoD expression. Further clarification is requested with regard to this amendment. In particular, although the amendment does not add new matter to the specification, the amendment does not make clear that the amendment of "myogenin" is a clear typographical error.

Claim Rejections - 35 USC § 112 –Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-24, 26-38 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for stimulating angiogenesis in a subject comprising:

injecting into a muscle tissue of the subject an isolated nucleic acid expression construct,

wherein the muscle tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding IGF-I and a 3' UTR,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked,

thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject.

The specification does not reasonably provide enablement for the breadth of the claims which encompass utilizing nucleic acid expression constructs that comprise any fragment of a myogenic promoter and any nucleic acid sequence encoding any fragments of IGF-I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 3/29/06.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of

the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that they have now amended the claims in accordance to what was indicated to be enabling by the Examiner and that one of ordinary skill in the art would understand that the claim language indicates that the nucleic acid sequence of the invention encodes IGF-I or functional biological equivalent thereof. Applicants argue that if the practitioner needed further guidance, the specification provides a specific definition on the term IGF-I or functional biological equivalent thereof (see p. 11, last ¶). In particular, Applicants argue that based on claim 17's limitation and support from the specification, one of ordinary skill would understand that a nucleic acid sequence that is 90% identical to SEQ ID NO: 1 should encode an IGF-1 amino acid having a specific biological activity, and that a nucleic acid that has 90% identity but does not encode IGF-I or its functional biological equivalent, and does not contain a specific biological activity, would not read on the instant claim. Applicants argue that thus, the claimed invention is enabled. See page 12 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. In particular, the Examiner notes that the claims as amended now recite expression of a nucleic acid sequence encoding IGF-I, or a functional biological equivalent therefore, wherein the IGF-I or functional biological equivalent is capable of binding to an IGF-I receptor. However, this amendment does not overcome the prior rejection of record, because the specification only describes working examples where human full-length wild-type IGF-I was delivered and expressed in muscle tissue.

With regard to Applicants' arguments that the now amended claim 17 is enabled, because one of ordinary skill would understand that a nucleic acid sequence that is 90% identical to SEQ ID NO: 1 "should encode an IGF-1 amino acid

having a specific biological activity" (see p. 12, 2nd ¶), these arguments are not persuasive, because Applicants' are arguing limitations that are not found in the claims. In particular, claim 17 does not recite a specific percent identity to SEQ ID NO: 1, the claim is much broader, and encompasses any nucleic acid sequence that encodes IGF-I, or a functional biological equivalent, that is capable of binding an IGF-I receptor. The specification provides no specific guidance or working examples as to how an artisan would practice the claimed invention with a nucleic acid encoding any IGF-I (e.g. any fragments or derivatives of IGF-I). It is reiterated that the state of the art, at the time of the claimed invention, teaches that IGF-I possesses cysteine residues that participate in disulfide bond formation and that said disulfide bond formation is important for proper protein folding and the resultant tertiary structure required for proper biological function, as taught by Milner et al (cited previously), for example (see Abstract; page 865, col. 1, paragr. 1). Applicants have now amended the claims to recite that the IGF-I or functional biological equivalent would be capable of binding the IGF-I receptor. This does not provide specific guidance to show the nucleic acid sequence(s) encompassed by the claims would be functional, with respect to the claimed invention, and the function of IGF-I to stimulate angiogenesis.

With regard to claims 18-21 and 24, Applicants have now amended the claims to recite specific biological functions of the myogenic promoter (claim 18); the encoded IGF-I or functional biological equivalent that is at least 85% identical to SEQ ID NO: 4 (claims 19-20); and the 3'UTR. These embodiments are not enabled for the following reasons:

Claim 18 encompasses a promoter that has up to 15% difference from SEQ ID NO: 3 and retains myogenic promoter activity. Following the analysis set forth in the prior Office action, SEQ ID NO: 3 contains 323 nucleotides, of which approximately 49 nucleotides could differ, given at least 85% identity. The specification teaches that SEQ ID NO: 3 encodes the muscle specific synthetic

promoter, SPc5-12 (see p. 42, ¶145). The specification does not teach what nucleotides or portions of the nucleotide sequence of this promoter are essential to the function of the promoter as a myogenic promoter. Applicants provide no specific analysis or guidance with regard to which nucleotides could differ from SEQ ID NO: 3 such that the resultant promoter would retain the myogenic promoter activity that could be used in context of the claimed invention, namely to stimulate angiogenesis.

Similarly, as stated in the prior Office action, the analysis of claim 24 reads on a nucleic acid construct wherein the entire IGF-I encoding nucleic acid fragment is replaced with a nucleic acid of any nucleotide composition. In other words, the nucleic acid sequence of SEQ ID NO:1 contains 5423 nucleotides and a nucleic acid sequence that is 90% identical to SEQ ID NO:1 would tolerate replacement of up to approximately 542 nucleotides. The nucleotide sequence encoding IGF-I being approximately 461 nucleotides, claim 24 reads on a nucleic acid construct that doesn't even encode IGF-I. The specification provides no guidance as to how an artisan would make or use the claimed invention as such.

In summary, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of expressing a nucleic acid in muscle tissue when said nucleic acid is operably linked to a myogenic promoter and the unpredictability of practicing the claimed invention with any IGF-I derivative. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Written description

Claims 17-24 and 27-38 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Applicants Arguments. Applicants argue that they have now amended claim 17 to include a structural limitation to a representative number of species for the large genus, namely, the IGF-I or functional equivalent is capable of binding to an IGF-I receptor. Applicants argue that one of ordinary skill in the relevant art would understand that IGF-I or IGF-I derivatives are so structurally mutated that do not bind the receptor, or do not fold correctly, or the tertiary structure is altered is excluded, because they would not provide a similar or biological function; however, functional biological equivalents analogs that have structural features that allow the analog to bind the IGF-I receptor also have similar function. Applicants argue that specific-specific IGF-I were known in the art at the time of filing, and that these references indicate significant homology between species. Applicants submit that the recitation of all these sequences or experimentation with many sequences already known in the art would have been unnecessary. Furthermore, one of ordinary skill at the time of the invention would have known that the IGF-I amino acid sequence is identical for humans, cows, dogs, horses and pigs, and that the nucleic acid sequence could be modified or different due to degeneracy of codons. Thus, Applicants argue that one of ordinary skill in the art could create a list of all degenerate variants of a nucleotide sequence for any encoded proteins using

programs readily available to the public at the time of filing. Applicants argue that the use of a construct encoding for human IGF-I or functional biological equivalents thereof, de facto enables many other species and derivatives of a genus without undue experimentation. Therefore, Applicants submit that human IGF-I that was used as a representative example can reasonably enable the broader genus. The amended claim adds the specific structural features of the IGF-I, or functional biological equivalent thereof, and its ability to bind an IGF-I receptor which distinguishes the claimed genus from other non-functioning members. See pages 13-14 of the Response.

Response To Arguments. These arguments have been fully considered, but are not persuasive. In particular, Applicants' arguments appear to be directed to "undue experimentation" to use a construct encoding for human IGF-I or functional biological equivalents thereof (see bottom of p. 13 of the Response), this is not pertinent to a *written description* rejection, which is the instant rejection. Written description is separate and distinct from the enablement requirement. See MPEP §2163. In particular, to satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the invention has *possession of the claimed invention.* Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

In the instant case, Applicants' claims encompass more than a nucleic acid sequence that encodes IGF-I. The claims are directed to a nucleic acid sequence encoding IGF-I, or a functional biological equivalent thereof, wherein the IGF-I or functional biological equivalent is capable of binding to an IGF-I receptor (claim 17); and more specifically, the encoded IGF-I, or functional biological equivalent thereof has an amino acid sequence of SEQ ID NO: 4, or SEQ ID NO: 4 with conservative amino acid substitutions and retains the function of inducing angiogenesis in the tissue of a subject (claim 20); and further, wherein the encoded IGF-I is a biologically active polypeptide, and the encoded functional biological equivalent of IGF-I is a polypeptide that has been engineered to contain a distinct amino acid sequence while simultaneously having similar or improved biological activity when compare to the IGF-I polypeptide (claim 37).

The specification's definition of "IGF-I or functional biological equivalent thereof" (see page 43, paragr. 0147 of the specification)does not provide any specific identifying characteristics to show that Applicants' had possession of the claimed invention. Furthermore, the specification's definition a functional biological equivalent encompasses any biomolecule that has a similar or improved biological activity when compared to IGF-I, this encompasses any polypeptide that could or could not have a structural relationship to IGF-I, as encoded by SEQ ID NO: 1. For example, this can encompass any biological equivalent that can bind to the IGF-I receptor (which is the only functional requirement in claim 17). Applicants have not described any functional biological equivalents to IGF-I, other than that which is encoded by SEQ ID NO: 4 to show that Applicants were in possession of the wide genus of polypeptides encompassed by the claims. Although one of skill in the art may know the sequence of IGF-I, this does not provide guidance for other molecules, which may have little or no similar identity to SEQ ID NO: 4, yet would be considered "biological equivalents" of IGF-I. It is not persuasive that Applicants' state that one could create a list of all degenerate variants of the IGF-I amino acid

sequence, because the claims encompass sequences that could potentially be unrelated to the IGF-I amino acid sequence.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, full-length human IGF-I is the only species whose complete structure is disclosed. While the genus encompasses a large number of variants and molecules that are functional biological equivalents of IGF-I the specification does not describe the complete structure of a representative number of species of the large genus.

The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. Cf. In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) (holding that a process could not render the product of that process obvious under 35 U.S.C. 103). The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405.

In conclusion, Applicant's disclosure of one species (i.e. full-length human IGF-I) of the claimed broad genus of functional biological equivalents of IGF-I is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The prior rejection of claim 17 is withdrawn in view of Applicants' amendment to the claims, which now provide positive steps that relate back to the preamble of the claim.

The prior rejection of claim 23 is withdrawn in view of Applicants' amendment to the claim, which now has deleted reference to a viral vector.

New rejections necessitated by amendment, appear below.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-21 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-21 and 24 are indefinite. This is a new ground of rejection, necessitated by Applicants' amendment, which now recites, in each of the claims "further comprising selecting". In particular, this amendment renders these claims indefinite, because it is unclear where the step of "further comprising selecting" relates to the independent claim. For example, claim 18 recites "further comprising selecting the myogenic promoter comprises..." this is grammatically incorrect, and unclear as to at which point one would further select a myogenic promoter. The independent claim recites injection of the nucleic acid construct into muscle tissues, and then describes the construct to be injected. It is unclear where this step would occur in the method. Similarly, claim 19 recites "further comprising selecting the encoded IGF-I". Although claim 17 recites that the nucleic acid construct comprises IGF-I, but it is unclear where a method step that would further comprising selecting the encoding IGF-I would relate to the method of claim 17. Claims 20-21 and 24 are similarly unclear for the same reasons as claims 18-19.

Claim Rejections - 35 USC § 102

The prior rejection of claims 17, 19-23, 31-38 under 35 U.S.C. 102(b) as being anticipated by Coleman et al **(Journal of Biological Chemistry, 270:12109-12116, 1995, IDS)** is withdrawn in view of Applicants' arguments and/or amendments to the claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 19-21, 31-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Alila *et al.* (**Hum. Gene Therapy**, 8: 1785-1795, October 10, 1997, cited as Reference 19 on Applicants' IDS, filed 5/27/04). This is a new ground of rejection, necessitated by Applicants' amendment to the claims, which now require injecting into *muscle tissue.*

The claims are directed to methods of stimulating angiogenesis comprising injecting into a muscle tissue of a subject an isolated nucleic acid expression construct; wherein the muscle tissue comprises cells; and the isolated nucleic acid expression construct comprises a myogenic promoter; a nucleic acid sequence encoding an IGF-I or functional biological equivalent thereof, wherein the IGF-I or functional biological equivalent is capable of binding to an IGF-I receptor; and a 3' untranslated region (3'UTR); wherein the isolated nucleic acid construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked; thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct that enables an *in vivo* expression activity for the encoded IGF-I or functional biological equivalent thereof stimulating angiogenesis in the tissue of the subject.

Alila *et al.* teach the construction of a plasmid (pIG0552), which contains the 5' portion of the chicken skeletal α-actin gene enhancer/promoter, which is operably linked to the human IGF-I cDNA, and flanked by the 3' portion of human growth hormone UTR (see page 1786, 1st col., 1st ¶ and Figure 1). They teach the purified plasmid was formulated with a complex with PVP (polyvinylpyrrolidone) and then intramuscularly injected into the hind limb of rats (see p. 1787, 1st col., Animal Injections). The muscle samples were then harvested and frozen at various time

points and analyzed for hIGF-I expression. Alila *et al.* teach that hIGF-I expression was found localized in the injected muscles (see p. 1790, col. 1-2, bridging ¶).

Accordingly, Alila *et al.* teach the claimed invention, because they teach intramuscular injection of a construct with a myogenic promoter (chicken skeletal α-actin), which is operably linked to a nucleic acid sequence encoding IGF-I, operably linked to a 3'UTR region, and they teach the expression of this plasmid construct localized to muscle tissue.

With regard to claims 19-21, the claims are written in the alternative, thus Alila anticipate these embodiments as follows:

1) Claim 19 recites selecting IGF-I *or* a functional biological equivalent, because Alila teach the cDNA sequence of IGF-I, they anticipate the claim.

2) Claim 20 recites selecting an encoded IGF-I *or* a functional biological equivalent that has an amino acid sequence of SEQ ID NO: 4, *or* SEQ ID NO: 4 with conservative amino acid substitutions; because Alila teach the sequence of IGF-I, they anticipate the claim.

3) Claim 21 recites that the 3' UTR comprises a nucleic acid sequence that is 85% identical to SEQ ID NO: 5 from a skeletal alpha actin gene *or* at least 85% identical from a human growth hormone gene and retains 3'UTR activity; because Alila teach the human growth hormone 3'UTR (which is 100% identical to a human growth hormone gene 3'UTR), they anticipate this claim.

Alila *et al.* further anticipate specific embodiments of the claims in that they teach delivery via a single administration (claim 31); delivery into somatic (muscle) cells (claim 32), which are diploid cells (claim 33): they show the expression of the encoded IGF-I (claim 34); that is expressed in tissue-specific cells (muscle cells) (claims 35-36); wherein the IGF-I is a biologically active polypeptide (claim 37); and that the subject is an animal (rat) (claim 38).

With regard to the requirement that the expression of the nucleic acid construct stimulate angiogenesis, the Examiner notes that, "Products of identical

chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

In the instant case, Alila *et al.* teach the steps of injection of a specific nucleic acid expression construct which fulfills the limitations of the claims; thus, the property of the nucleic acid, when expressed, is that that it stimulates angiogenesis.

Accordingly, Alila *et al.* anticipate the claims.

Claim Rejections - 35 USC § 103

The prior rejection of claims 17-24, 26-38 under 35 U.S.C. 103(a) as being unpatentable over Coleman in view of Draghia-Akli in view of Fewell *et al.* and Isner is withdrawn in view of Applicants' amendment to the claims which now require injecting the nucleic acid expression construct into a *muscle* tissue of a subject. A new rejection appears below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* as applied to claims 17, 19-21, 31-38 above in the §102 rejection, and further in view of van Deutekom *et al.* (Mol. Med. Today, 214-220, May 1998). This is a new ground of rejection, necessitated by Applicants' Amendment.

Alila *et al.* are summarized above. They do not specifically teach mixing the isolated nucleic acid expression construct with a transfection facilitating system before delivery (claim 22); or that the transfection facilitating system is a liposome or cationic lipid (claim 23). However, prior to the time of the claimed invention, van Deutekom teach that intramuscular injection of non-viral vectors – such as plasmid DNAs – which are encompassed by the instant claims, are shown to have low transfection efficiency, and that these efficiencies can be improved by using non-targeted liposomes and/or polylysine-condensed plasmid DNA (see p. 215, 1st col., 1st ¶, Non-Viral Vectors).

Accordingly, given the combined teachings of Alila *et al.* and van Deutekom, it would have been obvious for one of ordinary skill in the art to modify the method of Alila *et al.* to mix the isolated nucleic acid expression construct with a transfection-facilitation system, such as utilizing a liposome, as contemplated by van Deutekom, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as van Deutekom discuss the low transfection efficiency in intramuscular gene delivery, and suggest using non-targeted liposomes to improve efficiency.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 18, 24, 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* (cited above) in view of Draghia-Akli (cited previously), Fewell et al (cited previously) and Isner (cited previously). This is a new ground of rejection, necessitated by Applicants' Amendment.

Alila *et al.* is cited above. Alila *et al.* does not teach a myogenic promoter comprising a nucleic acid sequence that is at least 85% identical to SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12) (claim 18), does not teach a nucleic acid construct comprising the nucleotide sequence of SEQ ID NO:1 (claim 24 and 26) and does not teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells (claims 27-30).

Draghia-Akli teaches a myogenic promoter consisting of the nucleic acid of SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12). Draghia-Akli teaches a plasmid construct comprising the SPc5-12 promoter operably linked to a nucleic acid encoding human growth hormone releasing hormone (GHRH; page 1182, col. 2, paragr. 3). Draghia-Akli teaches intramuscular injection of said plasmid construct into pigs and then electroporating the injected muscle of said pig to more efficiently deliver said plasmid to the muscle cells (page 1180: col. 1, paragr. 4, line 1 to col. 2, line 10). Draghia-Akli teaches that said SPc5-12 promoter is a powerful synthetic muscle promoter that drives high level expression of operably linked heterologous nucleic acids in a muscle-specific manner (page 1180, col. 1, lines 1-2).

Fewell teaches instramuscular injection of plasmid DNA complexed with the charge polypeptide poly-L-glutamate into mice followed by electroporation. Fewell teaches that injection of a plasmid comprising a nucleic acid encoding factor IX and that injection of a plasmid comprising a nucleic acid encoding erythropoietin as such (i.e. forming a complex comprising said plasmids and poly-L-glutamate prior to injection) resulted in enhanced expression of said plasmids compared to when said

plasmids were injected as saline solution (i.e. when said plasmids were not complexed with poly-L-glutamate). Thus, Fewell teaches that intramuscular injection of plasmid DNA complexed with poly-L-glutamate followed by electroporation results in more efficient transfection of the cells within the injected muscle.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the method of Alila *et al.* with a reasonable expectation of success by: 1) interchanging the avian skeletal chicken skeletal α-actin promoter with the strong muscle-specific synthetic SPc5-12 promoter taught by Draghia-Akli, 2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell and 3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to modify the method of Coleman as such because: 1) Draghia-Akli teaches that the synthetic SPc5-12 promoter drives high level, muscle-specific expression of operably linked nucleic acids, 2) Fewell teaches that complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection and prior to electroporation results in enhanced uptake of said plasmid DNA and 3) both Draghia-Akli and Fewell teach that electroporating muscle after intramuscular injection of plasmid DNA results in enhanced uptake of said plasmid DNA. Increased cellular uptake of plasmid DNA and increased expression of operably linked nucleic acids contained within said plasmid would be advantageous when practicing methods of gene therapy. Thus, the claimed invention as a whole was *prima facie* obvious.

Further, it is noted that pAV2001 (i.e. SEQ ID NO:1 of the instant application) is a hybrid plasmid consisting of fragments of the plasmids taught by Alila (citing Coleman) and Draghia-Akli. The specification on page 42, lines 16-19 recites, "An Nco/HindIII fragment of a SIS II plasmid (Coleman et al., 1995),

containing the IGF-I cDNA and the skeletal alpha actin 3'UTR, was cloned into the NcoI/KpnI sites of pSP-HV-GHRH (Draghia-Akli et al., 1999) to generate pSP-IGF-I-SK3'UTR (pAV2001 – SEQID No.: 1)." Thus, an artisan of ordinary skill at the time of the invention would have realized with a reasonable expectation of success that the teachings of Coleman and Draghia-Akli could be combined to generate the plasmid DNA consisting of the nucleic acid sequence of SEQ ID NO:1.

Although neither Alila, Draghia-Akli or Fewell specifically state that IGF-I is an angiogenic factor, Isner teaches a method for stimulating angiogenesis in an ischemic muscle tissue in a human host comprising injecting into said tissue a DNA sequence encoding an angiogenic protein, wherein said DNA sequence comprises a promoter sequence, wherein the angiogenic protein is selected from a group of angiogenic proteins including insulin-like growth factor (IGF-I; claims 1 and 16; col. 4, lines 8-10, 23).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to utilize the methods of Alila, to intramuscularly inject a construct that comprises the construct as taught by Alila, Coleman and Draghia-Akli, and to modify this technique by electroporating the muscle after injection of the plasmid DNA, by methods taught by Fewell, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these modifications, as shown above, that Draghia-Akli teach a strong, muscle-specific promoter, and that complexing plasmid DNA with poly-L glutamate prior to intramuscular injection and electroporation after injection results in more efficient transfection of the cells within the injected muscle. The teachings of Isner provide additional motivation for an artisan of ordinary skill to use a nucleic acid encoding IGF-I to stimulate angiogenesis in muscle and further support that the claimed invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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